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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 09/613,887
Filing Date: July 11, 2000
Appellant(s): HOGAN, KIRK

David Casimir
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed June 9, 2005 appealing from the Office action mailed January 11, 2005.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal. It is noted that an appeal has been filed in 09/976,423 which identifies the instant application as a related appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

The amendment after final rejection filed on September 21, 2005 has been entered to correct the minor typographical errors.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

- Miller (Anesthesia, Vol. 2, pages 1323-1333, 1981)

- Quane et al (Human Molecular Genetics, Vol 3, No. 3, page 471-476, 1994)
- Acta Anaesthesiologica Scandinavica (Vol 39, page 139-141, 1995)
- La Du (Cellular and Molecular Neurobiology, Vol 11, No. 1, page 79-89, 1991)
- Pharmacogenetics (Chapter 4, pages 309-326, IDS #201)
- Evans et al (Science, Vol. 286, pages 487-491, October 1999)
- Poort et al (Blood, Vol 88, No. 10, page 3698-3703, 1996)
- Hoon et al. (US Pat. 6,057,105, May 2, 2000)
- Hacia (Nature Genetics Supplement. Vol. 21, pages 42-47, January 1999).

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

1. Claims 74-105 are rejected under 35 U.S.C. 103(a) as being unpatentable over Miller (Anesthesia, Vol. 2, pages 1323-1333, 1981) in view of Quane et al (Human Molecular Genetics, Vol 3, No. 3, page 471-476, 1994) or Acta Anaesthesiologica Scandinavica (Vol 39, page 139-141, 1995) and La Du (Cellular and Molecular Neurobiology, Vol 11, No. 1, page 79-89, 1991) or Pharmacogenetics (Chapter 4, pages 309-326, IDS #201) and Evans et al (Science, Vol. 286, pages 487-491, October 1999) or Poort et al (Blood, Vol 88, No. 10, page 3698-3703, 1996) and further in view of Hoon

et al. (US Pat. 6,057,105, May 2, 2000) and Hacia (Nature Genetics Supplement. Vol. 21, pages 42-47, January 1999).

Miller teaches screening a patient preoperatively to determine a risk for complications during a surgical procedure. Miller teaches that patients meet with the surgeon to prepare for surgery. Miller teaches that the surgeon often informs the patient of the anesthetic preoperative requirements and presents the patient with a letter. A sample letter is provided which illustrates the date of the surgery with the time, and instructions that "it is also important that your blood tests, urinalysis, and any other tests ordered by your doctor be completed two days before you are scheduled for surgery so that they can be reviewed by your anesthesiologist prior to surgery". Miller therefore teaches the importance of a blood test prior to surgery to identify any abnormalities.

Miller does not specifically teach analyzing the blood taken from the patient within two days prior to surgery for "two or more known genetic variations associated with two or more conditions".

However, Quane et al (herein referred to as Quane) teaches the detection of novel common mutations in ryanodine receptor gene (RYR1) in malignant hyperthermia (MH). Malignant hyperthermia (MH) is triggered in susceptible people by all commonly used inhalation anesthetics. Quane has identified Gly341Arg mutation which accounts for approximately 10% of Caucasian MHS cases (abstract). Quane specifically teaches that once an individual is diagnosed as being susceptible to MH, the anesthetics which trigger this syndrome can be avoided (page 471, col. 2). Quane also teaches that

Arg615Cys is a substitution found in 3-5% of human MH families investigated (page 472, col. 1); Arg163Cys is a substitution found in 2-3% of MHS cases. Furthermore, three other rare mutations have been reported in the RYR1 gene which are in three isolated MHS and/or CCD cases. Quane teaches that patients which have not been indicated as MH normal should always be considered MHS clinically to avoid any possibility of the individual reacting to a triggering agent during anesthesia. Misdiagnosis of MHS individual as MHN can be lethal if such a patient is exposed to triggering agents (page 474, col. 1). Quane teaches that the mutation reported satisfies the genetic criteria necessary for demonstration of a causal mutation and as such this mutation should be of significant value for MHS diagnosis by genetic means (page 474, col. 1). Quane analyzes genomic DNA from peripheral blood for the presence of the mutations (page 474, col 2).

Acta Anaesthesiologica Scandinavin (referred to as AAS) teaches that certain variants have a dramatic degree of resistance to the drug, succinylcholine (SC), because they destroy it so rapidly. AAS teaches that individuals show no regular metabolic disorder unless SC or mivacurium is given such that the condition is provoked. BchE mutations are dibucaine resistant, fluoride resistant or silent. SC and mivacurium are potentially toxic in people with BchE deficiency. AAS teaches that the principles of molecular biology tests and their application to BchE variants are well illustrates and anesthesiologists need to keep up to date about these applications. AAS also teaches that other hereditary conditions of special interest to anesthesiologists,

such as malignant hyperthermia, may be diagnosed by similar methods in a few years (page 141).

La Du et al (herein referred to as La Du) teaches butyrylcholinesterase variants which have been found in individuals who have responded abnormally to the muscle relaxant succinylcholine. Variants with increased activity are resistant to succinylcholine and may require two or three doses to achieve the desired state of paralysis (page 80).

Pharmacogenetics teaches polymorphisms of desbrisoquine hydroxylase (Cytochrome P4502D6). The structures of CYP2D gene clusters are provided. The poor metabolizers are depicted. Pharmacogenetics teaches that for drugs such as codeine and encainide it is the PM subjects who may experience therapeutic failure (page 317, col. 1). Codeine is ineffective analgesic in the 5-10% of the population who have a PM phenotype. The discovery and identification of each of these conditions has saved some lives and may prevent future fatalities or morbidities.

Evans et al (herein referred to as Evans) teaches the drug-metabolizing enzyme debrisoquine hydroxylase (CYP2D6) is polymorphic. Evans teaches that "inherited differences in drug-metabolizing capacity are generally monogenic traits and their influence on the pharmacokinetices and pharmacologic effects of medications is determined by their importance for the activation or inactiviation of drug substrates (page 487, col. 2). Evens also teaches "the effects can be profound toxicity for medications that have a narrow therapeutic index and are inactivated by a polymoprhic enzyme (for example, mercaptopurine, azathioprine, thioguanine, and fluorouracil) or reduced efficacy of medications that require activation by an enzyme exhibiting genetic

polymorphism (such as codine)" (page 487, col. 3). Evans illustrates in Figure 2, drug-metabolizing enzymes known to exhibit genetic polymorphisms with incontrovertible clinical consequences. Further, severe and potentially fatal hematopoietic toxicity that occurs when thiopurine methyltransferase-deficient patients are treated with standard doses of azathioprine or mercaptopurine. Evans teaches that "many opioid analgesics are activated by CYP2D6 rendering the 2-10% of the population who are homozygous for nonfunctional CYP2D6 mutant alleles relatively resistant to opioid analgesic effects. Thus is it not surprising that there is remarkable interindividual variability in the adequacy of pain relief when uniform doses of codeine are widely prescribed" (page 489, col. 1). Evans teaches that individualizing drug dosages can improve clinical outcome (page 491, col. 1).

Poort et al (herein referred to as Poort) teaches an 20210 AG gentoype of the prothrombin gene which is a candidate for venous thrombosis in patients. It is well known in the art that venous thromboembolism can occur without apparent cause, after surgical procedures or trauma. Poort also teaches that factor V Leiden is the most common hereditary risk factor for thrombosis. Poort teaches two genetic markers which are associated with thrombosis.

Moreover, Hoon et al. (herein referred to as Hoon) teaches the benefits of using multiple markers in detection assays. Hoon teaches using multiple markers provides increased sensitivity (abstract). Hoon teaches that marker combinations may be developed, which are particularly sensitive to the effect of therapeutic regimens on disease progress such that patients may be monitored (col. 4, lines 65-68). In a

particular example, Hoon demonstrates that number of markers was studied and that using four markers was significantly better than a single marker alone (col. 21).

Additionally, Hacia teaches mutational analysis using oligonucleotide microarrays. Hacia teaches that arrays of 1,480 oligonucleotide probes were designed to detect 37 known mutations, probes were spotted on surfaces to detect mutations in HBB, and BRCA1. Hacia teaches that arrays of 135,000 probes were used to interrogate the entire 16.6kb human mitochondrial genome from ten samples (page 44, col. 1). Chips have also been used for the simultaneous genotyping of 500 markers (page 45, col. 1). Hacia teaches that chips allow for unprecedented throughput in mutational analysis with a high degree of accuracy (page 46, col. 2).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have sampled patients prior to subjecting the patient to anesthetics, as taught by Miller, to determine whether they were at risk of MH, a dramatic degree of resistance to the drug, succinylcholine (SC), resistant to succinylcholine, desbrisoquine hydroxylase, or venous thromboembolism, as taught by Quane, Acta Anaesthesiologica Scandinavica, La Du , Pharmacogenetics, Evans or Poort . Miller teaches that it is routine to sample patients blood to analyze the blood for abnormalities including hematocrit levels. Miller teaches that "the laboratory evaluation should be available for review by the anesthesiologist prior to or at the time he first sees the patients preoperatively so that any questions regarding the patient's status should be resolved then and if not resolved the surgery should be delayed" (page 1325). Quane provides three examples of common mutations within the RYR1 gene which are

associated with MH and which trigger MH syndrome during anesthesia, and potentially death. Quane specifically states that "once an individual is diagnosed as being susceptible to MH, the anesthetics which trigger this syndrome can be avoided" (page 471, col. 2). AAS teaches that SC and mivacurium are potentially toxic in people with BchE deficiency. La Du et al teaches butyrylcholinesterase variants which have been found in individuals who have responded abnormally to the muscle relaxant succinylcholine and the variants with increased activity are resistant to succinylcholine and may require two or three doses to achieve the desired state of paralysis (page 80). Pharmacogenetics teaches that codeine is ineffective analgesic in the 5-10% of the population who have a PM phenotype. Evens also teaches "the effects can be profound toxicity for medications that have a narrow therapeutic index and are inactivated by a polymoprhic enzyme (for example, mercaptopurine, azathioprine, thioguanine, and fluorouracil) or reduced efficacy of medications that require activation by an enzyme exhibiting genetic polymorphism (such as codine)" (page 487, col. 3). Additionally, Port teaches that factor V Leiden is the most common hereditary risk factor for thrombosis and two genetic markers which are associated with thrombosis.

Thus, the ordinary artisan would have been motivated to test patients within two days prior to surgery for mutations within the RYR1, CYP2D6, Prothrombin, BCHE genes for the expected benefit of determining whether the patient possessed any mutations which were linked to the known condition of MH to avoid any fatal reaction to the anesthesia, for example. The ordinary artisan would have recognized that blood samples are routinely taken within two days prior to surgery and therefore to minimize

inconvenience to the patient, the blood sample taken would also be an ideal sample for testing the patient for genetic abnormalities within RYR1. The ordinary artisan would have clearly recognized the benefit of testing an individual prior to surgery and subjection to the anesthesia for known genetic markers associated with a condition which was triggered by anesthetics.

Moreover, given the teachings of Hoon and Hacia that sampling multiple markers provides increase sensitivity, the ordinary artisan would also be motivated to have sampled additional markers which are associated with complications in surgery. Therefore, the skilled artisan would have additionally analyzed a patient for a dramatic degree of resistance to the drug, succinylcholine (SC), resistant to succinylcholine, desbrisoquine hydroxylase, or venous thromboembolism, as taught by Acta Anaesthesiologica Scandinavica, La Du, Pharmacogenetics, Evans or Poort. Given the state of the art with relation to known markers and detecting the markers as indicative of certain disease which either trigger episodes when exposed to anesthetics, or are poor metabolizers or potentially cause thrombosis are well known. The ordinary artisan would have been motivated to have screened individuals within two days prior to surgery to determine the genetic composition of the individuals to provide individualized diagnosis. Thus, the ordinary artisan would have been motivated to test patients within two days prior to surgery for mutations within any of the known genes for known mutations which are associated with known conditions for the expected benefit of determining whether the patient possessed any mutations which were linked to the known conditions such that the clinician may avoid any adverse reactions to the surgical

procedure. It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have modified the vast number of teachings, as exemplified by the extremely voluminous Information Disclosure Statement filed, to screen individuals prior to surgery for several genetic markers which are indicative of any number of conditions which are caused by anesthesia or are a result of anesthesia. Hacia teaches that large numbers of probes are placed on arrays for the express benefit of high-throughput mutational analysis with a high degree of accuracy (page 46, col. 2). The ordinary artisan would have recognized that the art provides a large number of single nucleotide polymorphisms or other variations which are indicative of conditions. The benefit of screening individuals for several of these prevalent mutations which are related to surgery would have allowed the anesthesiologist to determine whether plausible substitutes may be provided to patients which would not cause these conditions to arise. Specifically, detection of RYR1 polymorphisms which are associated with MH would indicate to the anesthesiologist that drugs which trigger the episodes should be avoided. Moreover, codeine should be administered with care to individuals having certain BchE mutations. Combining more than one screening method to determine the genomic profile of a patient would have provided the anesthesiologist with a more complete picture of the patients genetic make-up. As suggested in many of the articles, individual treatment and screening is ideal for analysis of the genetic make-up of patients.

With respect to the claims drawn to invasive and non-invasive surgery, anesthesia and codine, for example are administered routinely in each of these situations.

With respect to the claims drawn to specific numbers of markers, for example 5 and 10 or more mutations, the skilled artisan would be motivated to screen makers which were well known at the time of the art simultaneously or in tandem for the benefits of providing the most complete amount of information possible. Hacia specifically teaches that arrays to detect mutations of approximately 500 were known in the art at the time the invention was made.

(10) Response to Argument

Would it have been obvious to the ordinary artisan to screen for known genetic mutations in the art known to trigger negative syndromes/effects in response to anesthetics prior to providing anesthetics before surgery?

The Appellant traverses the rejection. The response filed January 2004, July 23, 2004 and the brief filed September 21, 2005 asserts that the cited art fails to establish prima facie obviousness. The claims are drawn to testing two or more nucleic acid markers in two or more genes associated with two or more conditions. The Appellant asserts that the Examiner has failed to establish a prima facie case of obviousness. This argument has been thoroughly reviewed, but is not found persuasive. The prior art teaches

- A method of performing perioperative screening to provide biological information about the patient within 72 hours of the surgery (Miller)
- Once an individual is diagnosed as being susceptible to MH, the anaesthetics which trigger this syndrome can be avoided (Quane). Mutations are taught which are associated with MH.
- Numerous mutations in numerous genes which are associated with toxicity, decreased or increased efficiency, ineffective to various operative drugs (Quane, De Lu, AAS, Poort, Evans, for example)
- Methods using multiple markers provide increased sensitivity over methods employing single markers (see Hoon)
- Arrays for high-throughput and highly accurate mutational analysis which may be used for as many as 500 mutations (Hacia).

The examiner has set forth a prima facie case which combines all of the teachings and motivations specifically enumerated in the art to obtain the claimed invention as a whole (see rejection above). The express teaching in Quane that "Once an individual is diagnosed as being susceptible to MH, the anesthetics which trigger this syndrome can be avoided" provides explicit motivation for testing individuals prior to anesthetics to avoid triggering MH. The ordinary artisan would have been motivated to have avoided triggering MH by performing the genetic testing taught by Quane. Similarly, the ordinary artisan would have been motivated to have not administered SC and mivacurium to people with BchE deficiency because the art teaches they are

potentially toxic. The ordinary artisan would have been motivated to have screened for BCHE deficiency to ensure that they were not providing a potentially toxic drug to their patient. Third, the ordinary artisan would have been motivated to screen for butyrylcholinesterase variants ensure that their patients received the necessary dose of relaxant succinylcholine to achieve the desired state of paralysis. Fourth, since individuals with poor metabolism experience therapeutic failure to codeine, the discovery and identification of polymorphisms in desbrisoquine hydroxylase (Cytochrome P4502D6) saved some lives and may prevent future fatalities or morbidities. The ordinary artisan would be motivated to prevent fatalities and morbidities by testing for polymorphisms in genes. Fifth, given the teachings in the art that "the effects can be profound toxicity for medications that have a narrow therapeutic index and are inactivated by a polymoprhic enzyme (for example, mercaptopurine, azathioprine, thioguanine, and fluorouracil) or reduced efficacy of medications that require activation by an enzyme exhibiting genetic polymorphism (such as codine)" (page 487, col. 3). Further, severe and potentially fatal hematopoietic toxicity that occurs when thiopurine methyltransferase-deficient patients are treated with standard doses of azathioprine or mercaptopurine. Evans teaches that individualizing drug dosages can improve clinical outcome (page 491, col. 1). The ordinary artisan would be motivated to avoid profound toxicity, reduced efficacy or fatality by testing for polymorphisms. Finally, genetic markers for venous thrombosis in patients have been identified. The ordinary artisan would have been motivated to screen for genetic

markers know to be associated with venous thromboembolism to enable early detection and avoid the serious effects.

Overall, the prior art provides a large body of art teaching mutations which are associated with diseases or conditions. The ordinary artisan would have been motivated to have assayed for genetic markers prior to surgery to enable the detection of markers which are negatively associated with surgical conditions so that the conditions may be avoided. Miller teaches that blood samples are taken within 72 hours prior to surgery. The ordinary artisan would have been motivated to have used the blood sample drawn at this point to analyze additional genetic markers such as those taught in the art. Since a blood sample was being taken 72 hours prior to surgery, the ordinary artisan would have been motivated to have avoided an additional blood draw and would have been motivated to have used the blood sample take during this period of time. Minimizing the unneeded discomfort of a patient is of considerable concern by professionals in the medical field.

On page 15 of the brief filed September 2005, the Appellant asserts that the combination of references does not teach all elements of the claims. This argument has been thoroughly reviewed, but is not found persuasive because the combination of references teaches obtaining a set of information about the patients genes. The specification, page 23, lines 6-10, specifically state that a "genomic profile" refers to a set of information about a given "subject's" genes (e.g., the presence or absence of a specific set of mutations or "SNPs"). The combination of references provides this element of information following analysis. While the references do not use the words

"genomic profile" it is clear from the specification that this "genomic profile" is a set of information about a patients genes. Quane, Acta, LaDu, Pharmacognentics, Evans and Poort each teach assaying for mutations or SNPs which give information about a subject's genes. Thus, each of these references is directed at providing a genomic profile, as required by the instant claims.

The brief then lists a large majority of the claims and indicates the limitations are not in the combination of references.

- Claim 76, 96- Administering anesthesia would trigger the same possible syndromes, for example MH as taught by Quane whether the surgical procedure to be performed is invasive or non-invasive. It is the anesthesia that causes the syndrome that would be ideally avoided, as taught by Quane. See second to last paragraph of rejection above addressing this issue.
- Claim 78- Avoiding the triggering of a syndrome that is initiated by anesthesias is taught by Quane.
- Claim 81- Obtaining the information regarding the genomic profile or the presence or absence of a mutation before surgery and before administering an anesthetic would occur prior to the symptoms of the syndrome which is triggered by anesthesia would occur, i.e. is presymptomatic diagnosis.
- Claims 83, 91- As provided above, AAS teaches that SC and mivacurium are potentially toxic in people with BchE deficiency. La Du et al teaches butyrylcholinesterase (BchE) variants which have been found in individuals who have responded abnormally to the muscle relaxant succinylcholine and the

variants with increased activity are resistant to succinylcholine and may require two or three doses to achieve the desired state of paralysis (page 80). Pharmacogenetics teaches that codeine is ineffective analgesic in the 5-10% of the population who have a PM phenotype of CYP2D6. Evens also teaches CYP2D6 that "the effects can be profound toxicity for medications that have a narrow therapeutic index and are inactivated by a polymoprhic enzyme (for example, mercaptopurine, azathioprine, thioguanine, and fluorouracil) or reduced efficacy of medications that require activation by an enzyme exhibiting genetic polymorphism (such as codine)" (page 487, col. 3). Additionally, Port teaches that factor V Leiden (F5) is the most common hereditary risk factor for thrombosis and two genetic markers which are associated with thrombosis. The art of record clearly teaches mutations in two or more genes associated with two or more conditions, as discussed above.

- Claims 84-85, 92-93- As discussed in the rejection, Hacia teaches chips have also been used for the simultaneous genotyping of 500 markers (page 45, col. 1). Hacia teaches that chips allow for unprecedented throughput in mutational analysis with a high degree of accuracy (page 46, col. 2). See final paragraph of rejection above, also.
- Claims 86, 98, 103, 105- The express teaching in Quane that "Once an individual is diagnosed as being susceptible to MH, the anesthetics which trigger this syndrome can be avoided" provides explicit motivation for testing individuals prior to anesthetics to avoid triggering MH". The ordinary artisan would have been

motivated to have avoided triggering MH by performing the genetic testing taught by Quane. Similarly, the ordinary artisan would have been motivated to have not administered SC and mivacurium to people with BchE deficiency because the art teaches they are potentially toxic. The ordinary artisan would have been motivated to have screened for BCHE deficiency to ensure that they were not providing a potentially toxic drug to their patient. Third, the ordinary artisan would have been motivated to screen for butyrylcholinesterase variants ensure that their patients received the necessary dose of relaxant succinylcholine to achieve the desired state of paralysis. Fourth, since individuals with poor metabolism experience therapeutic failure to codeine, the discovery and identification of polymorphisms in desbrisoquine hydroxylase (Cytochrome P4502D6) saved some lives and may prevent future fatalities or morbidities. The ordinary artisan would be motivated to prevent fatalities and morbidities by testing for polymorphisms in genes. Fifth, given the teachings in the art that "the effects can be profound toxicity for medications that have a narrow therapeutic index and are inactivated by a polymoprhic enzyme (for example, mercaptopurine, azathioprine, thioguanine, and fluorouracil) or reduced efficacy of medications that require activation by an enzyme exhibiting genetic polymorphism (such as codine)" (page 487, col. 3). Further, severe and potentially fatal hematopoietic toxicity that occurs when thiopurine methyltransferase-deficient patients are treated with standard doses of azathioprine or mercaptopurine. Evans teaches that individualizing drug

dosages can improve clinical outcome (page 491, col. 1). The ordinary artisan would be motivated to avoid profound toxicity, reduced efficacy or fatality by testing for polymorphisms. Finally, genetic markers for venous thrombosis in patients have been identified. The ordinary artisan would have been motivated to screen for genetic markers know to be associated with venous thromboembolism to enable early detection and avoid the serious effects. By avoiding the use of the agents which trigger the syndromes/effects, the ordinary artisan would have used the information (i.e. genomic profile) for selection of conditions for a surgical procedure. Furthermore, each of these syndromes direct the ordinary artisan to dosages for poor metabolizers (PM) or monitoring for thrombosis patients, for example.

These elements asserted to be missing elements by the brief had been provided in the rejections of record, but for extreme clarity have been reiterated above.

On page 17 of the brief filed September 2005, the Appellant states that the combination is not permissible because the art does not provide motivation to make the combination. The Appellant, stated "at best, Quane provides motivation to test patients after surgery for polymorphisms in a single gene for a single condition." This argument has been thoroughly reviewed, but is not found persuasive because Quane provides the motivation to avoid triggering of a condition which has been associated with a mutation. Quane, for example teaches that "once an individual is diagnosed as being susceptible

to MH, the anaesthetics which trigger this syndrome can be avoided." This explicit teaching to avoid anaesthetics which trigger MH is motivation to avoid administering anesthetics to patients with particular mutations. Taking additional known mutations which have been associated with conditions that are related to surgery or anesthesia, for example, would have been desirable to avoid the respective negative effects they have. Quane teaches "avoiding" particular anesthetics upon diagnosis of susceptibility. It logically follows that there are two times to test for polymorphisms, before a surgery or after a surgery. The art teaches that many mutations are associated with death due to anesthesia or additional conditions which inflict pain or suffering on the individual. While one may want to investigate after death or after a survival of a clinical episode of MH, it is more likely that the ordinary artisan would want to prevent death or pain and suffering inflicted due to the response to anesthesia. Quane teaches that once the individual is diagnosed as being susceptible to MH, the anesthetics which trigger the syndrome can be avoid. Quane thus contemplates and suggests avoiding death and pain and suffering. Since Quane also teaches that "the subclinical nature of MH makes its early diagnosis difficult" the ordinary artisan would turn to genetic detection of polymorphisms for diagnosis of MH.

The brief, page 19 states that Quane makes no mention of any other gene or condition. This argument has been thoroughly reviewed. The rejection above under 103 clearly indicates that Quane is directed to a single gene and a single condition, however, when considering the art as a whole at the time the invention was made, including the extremely large IDS provided by applicant, the number of genes,

mutations and conditions was well established. The examiner acknowledges, while the particular teachings of Quane are directed to MH, using genetic information to prevent or avoid certain conditions is broadly taught by Quane. Thus, the combination of references is used to illustrate that there are numerous polymorphisms and conditions associated in the art and to avoid or prevent the conditions, analysis of the polymorphism prior to surgery would be suggested. Multiplexing or arraying more than one mutation was well known in the art at the time the invention was made (see Hoon and Hacia). The ordinary artisan would have been motivated to have selected two or more markers taught in the art to be associated with negative perioperative aspects since Hoon teaches two markers is more significant than a single marker. Further, Hacia provides a clear means for assaying for more than one marker, i.e. an array. The ordinary artisan would have a reasonable expectation of success of assaying for more than one marker on an array since the prior art performs as many as 500 markers on a single array.

The Appellant asserts that Quane fails to teach that samples are tested in the perioperative period (see page 22 of Brief). This argument has been thoroughly reviewed, but is not found persuasive because Miller is used in the combination to show obviousness. The Appellant argues that Quane does not teach or suggest that anyone should be screened prior to surgery. This argument has been thoroughly reviewed, but is not found persuasive because the claim is not directed to patients who "are believed to be healthy going into the test." The claim is drawn to a patient. The response asserted that Quane does not "clearly recognize the benefit of testing prior to surgery."

The passage of Quane teaches that "once an individual is diagnosed as being susceptible to MH, the anesthetics which trigger this syndrome can be avoided." It is unclear how anesthetics which trigger this syndrome could be avoided if not diagnosed prior to surgery and/or administration of the anesthesia. Quane's patients have not been tested prior to surgery, however Quane provides clear motivation to test patients prior to surgery to avoid triggering the response to anesthesia. It the patient is not tested prior to surgery, but tested after surgery, the response to the anesthesia could not be avoided. Thus, Quane must be suggesting to test prior to surgery.

The brief asserts that the interpretation of Quane is inflate and any claims directed to the use of genetic information for the prevention or avoidance of any condition or any syndrome are rendered obvious by Quane after 1994. This argument has been thoroughly reviewed. It is the examiner's position that any known mutation at the time the invention was made, that was known to cause a condition or syndrome would render obvious the avoidance or prevention of the condition based on the genetic analysis of the known mutation obvious. This is not to say that new mutations or new associations of the old mutations with disease would be obvious. This would be an entirely different analysis and this is not an analysis required in the instant case, since it is clear from the record, applicants are claiming old mutations already associated with diseases. However, taking old information about genetic associations and wanting to prevent or avoid the syndromes or conditions they have already been associated with would be obvious. Here, the known mutation of RYR1 with the known association with MH would be obvious to want to prevent or avoid MH, as specifically taught by Quane.

Once the ordinary artisan has knowledge of a specific mutation is associated with a specific condition, it would be obvious to want to screen for the specific mutation to specifically avoid or prevent the condition. It is analogous to a person placing their hand on a hot stove. Once they know placing their hand on the hot stove causes a burn or "ouch", it would be obvious to the person not to touch the hot stove unless they wanted the known result of a burn or "ouch". It is much the same, once the person knows they have a mutation which will trigger a syndrome or condition, they would want to avoid or prevent the known syndrome or condition. In the particular instance of Quane, once an patient knows they have a RYR1 mutation that triggers a fatal disorder of skeletal muscle in response to commonly used inhalational anesthetics, the ordinary artisan would be motivated to want to avoid or prevent this condition (i.e. a fatality).

The response asserts that "preventing death and/or pain and suffering" is not the law under 103. This argument has been thoroughly reviewed. The Examiner agrees that 103 rejections do not require prevention of death and/or pain or suffering. It would be absurd to require such a standard in the computer art or fishing apparatus art, for example. However, the Examiner does assert that it is a strong motivation. The ordinary artisan would have been motivated to prevent something known to cause pain, suffering or death. As in the instant case, the ordinary artisan would have been motivated to have prevented administering a drug known to cause pain, suffering or death. Quane, in 1994, prior to the date of the instant application, stated that "once an individual is diagnosed as being susceptible to MH, the anesthetics which trigger this syndrome can be avoided." Thus in 1994, prior to the instant invention, the artisan was

attentive to the need to prevent and avoid events which may trigger death and/or pain and suffering. The examiner is unclear why the Appellant would not find that preventing death and/or pain and suffering would be a motivation recognized by one of ordinary skill in the art at the time the invention was made. The ordinary artisan would not only have been motivated to have prevented MH, a fatal autosomal dominant disorder of skeletal muscle which is triggered in susceptible people by all commonly used inhalational anesthetics, but would have also made an effort to prevent additional complications, disorder or diseases which are associated with know polymorphisms.

The Appellant asserts that evidence directly refutes the Examiner's rejection (see page 24 of brief). The Appellant refers to previously submitted references, peer reviews, Declaration and a practice Advisory. Each of these documents was previously considered. As addressed previously, the application for a grant entitled "Perioperative Genomic Profiles" to the Anesthesia Patient Safety Foundation (APSF) and was rejected by a panel of experts because "the state of the art teaches that such methods should not be carried out". Based upon the committees excerpt, the committed states that "the committee's concern and reason for not funding the study rested on a few factors. It is a basic science study without clear clinical value. In the values equation the committee members considered the study might improve the quality but the cost could be very high". While Appellants are arguing that the art is not routinely doing perioperative analysis, this is not the standard for obviousness. It is noted that the claim does not require "routine perioperative analysis." There is no requirement that the method be performed routinely. The claim is drawn to a method of perioperatively

screening a patient. There are many factors, such as family history, abnormal test results which may motivate a patient or physician to perform a screening method on a particular patient. As provided by the statute of 103,

> "A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made."

The statute does not provide that cost is a factor in considering non-obviousness. The committee does not appear to be establishing that given the art at the time of filing, that the invention was non-obvious, but the committee rather appears to be indicating that they do not think that the idea is a cost effective study. The committee has stated that "as anesthesia practice has moved toward determining the ratio or quality to cost, this study seems to be going in the opposite direction". This statement is directed to the economical benefits of sampling individuals prior to surgery not the obviousness of studying individuals prior to surgery. Furthermore, the factors considered when determining whether to fund a particular study are completely different than the factors considered in determining that an invention is legally patentable. Grants are often funded because they offer an immediate use, return on value or information that the community may build upon. These are not the criteria which must be met to obtain a patent or to show non-obviousness of the prior art references. The Appellant argues that "this objective evidence of non-obviousness, confuses the fact of non-obviousness ("it would take the issue of patient safety in a new direction"), with the reasons for non-obviousness i.e. cost, confidentiality, ethics. The examiner agrees that the reasons, i.e.

cost effectiveness, etc. are immaterial to the finding of non-obviousness, therefore, the reasons given in the grant study are not material to the finding of non-obviousness. The Appellant argues that the Examiner is distracted by cost and economic benefit analysis (page 21 of response). This argument has been thoroughly reviewed, but is not found persuasive because the examiner provide analysis as to why cost is not a consideration in determining obviousness.

The Appellant provides three references directed to the proposition that routine perioperative testing is unnecessary. First, Gregory teaches that value of routine preoperative screening tests for healthy infants and children has been questioned. Gregory teaches that "routine preoperative hemoglobin or hematocrit determinations have been recommended in the past, and have been or still are required by law in some jurisdictions. However, there are a few data to support the practice of subjecting every healthy child to a painful fingerprick or venipuncture." (page 184, col 1). While this passage illustrates that individuals may be questioning the need for blood tests prior to surgery many clinicians continue to sample blood and others are required to by law. Additionally, it is noted that in the event there is a trend to not perform preoperative screening tests, the invention is considered at the time the invention was made. Gregory was a paper from 2002 which was two years after the invention was made. Therefore, in 2000, public policy deems it important to perform preoperative blood analysis.

Similarly, Kirby teaches that routine laboratory screening tests are not cost-effective and are often inefficient. While routine screening has not yet reached the point

of being cost effective and highly efficient, the cited art still provides suggestion that with regard to the RYR1, BchE, prothrombin, etc. genes, testing prior to surgery would be certainly advantageous since mortality and complications may be avoided. While it is clear that many in the medical field do not believe that routine genetic testing provides sufficient valuable information to warrant its cost, this does not imply that the art has not conceived of or thought about the perioperative genetic testing. Once again, the claims are not drawn to routine testing as continually argued by the Appellant. While the art may assert that no perioperative testing is necessary for males who are less than 40, this is not any support that perioperative testing is not necessary for other patients who may be deemed at risk or outside the criteria suggested. The claims are not limited to males less than 40 years of age who are undergoing surgery with minimal expected blood loss.

The Appellant cites Hopkins to support, "the complexity of the molecular genetics of MH precludes DNA-based diagnosis at present. Thus, a modern analysis of the molecular genetics of MH concludes that DNA-based testing for MH is precluded and not desirable". The claims are drawn to detecting two or more genetic markers to generate a genomic profile useful in selecting perioperative course of action. The claims are not drawn to diagnosing MH. The claims are drawn to screening a patient perioperatively to determine a risk for complications; a method for selecting conditions for a surgical procedure; a method of screening a patient perioperatively to determine a risk for complications during said surgical procedure.

With respect to what the ordinary artisan would have recognized or appreciated, Quane teaches that once an individual is diagnosed as being susceptible to MH, the anesthetics which trigger this syndrome can be avoided. Quane is at least an ordinary artisan if not a skilled artisan. Quane clearly recognized the benefit of testing an individual prior to surgery to avoid triggering MH. Thus, the skilled artisan did recognize the benefit of screening individuals prior to surgery to avoid known conditions triggered by particular mutations or markers in genes.

The second declaration of Kirk Hogan, filed July 8, 2002, has been thoroughly considered, but found not persuasive. The declaration asserts that the state of the art has not tested subjects for genetic markers during the perioperative period. The declaration reviews a Practice Advisory for Preanesthesia Evaluation: A report by the American Society of Anesthesiologist Task Force on Preanesthesia Evaluation". The declaration asserts that no perioperative genetic testing of any kind is advocated, discussed or mentioned. This silence with respect to genetic testing does not mean that the testing would be unobvious. While the article may not specifically consider genotypes for preanesthesia evaluation does not provide evidence that the combination of the cited references do not provide the legal standard for obviousness. The teachings of the article are not directed to the non-obviousness of the invention. The examiner has set forth objective evidence in the form of references to establish a prima facie case of obviousness. The Appellant has selected certain passages from the evaluation which do not appear to represent the full teachings of the reference. The Practive Advisory for preanesthesia evaluation states that the study is intended to assist

decision-making in areas of patient care, but not intended as guideline, standards or absolute requirements. The evaluation may be "adopted, modified or rejected according to clinical needs and constraints (abstract). Moreover, preoperative tests may be indicated for various purposes including discovery or identification of a disease or disorder that may affect perioperative anesthetic care. It is noted that MH as taught by Quane is a disorder which will affect preoperative anesthetic care. Therefore, the reference does not appear to support the assertion that preoperative care precludes the testing of genetic markers. "The Task Force agrees that preoperative tests may be ordered, required, or performed on a selective basis for purposes of guiding or optimizing perioperative management. The indications for such testing should be documented and based on information obtained from medical records, patient interview, physical examination and type and invasiveness of the planned procedure" (page 490, col 1-2). Moreover, the Task force "believes that there is insufficient evidence to identify explicit decision parameters or rules for ordering preoperative tests on the basis of specific clinical characteristics" (page 490, col 1-2). Note 4, states that "selective preoperative tests (i.e., tests ordered after consideration of specific information obtained from sources such as medical records, patient interview, physical examination and the type of invasiveness of the planned procedure and anesthesia) may assist the anesthesiologist in making decisions about the process of preoperative assessment and management (page 493, col. 1). Therefore, based upon the teachings of the reference as a whole, the reference does not state that preoperative tests should not be done.

Thus, for the reasons above and those already of record, the rejection is maintained.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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